REMARKS

Claims 26-40 and 94-105 are pending in the application prior to entry of amendments submitted herewith, and all of those claims stand rejected. By amendment herewith new Claims 106-109 are being added. None of the amendments introduce new matter, and all of the amendments are made without prejudice to or disclaimer or dedication of any subject matter, and a right is specifically reserved to file continuation and/or divisional applications claiming any subject matter disclosed in the application.

Rejection Under 35 U.S.C. §103

Claims 26-40 and 94-105 have been rejected under 35 U.S.C. §103(a) based on an assertion of unpatentability over Debenedetti et al. (U.S. Patent No. 6,063,910) in view of Manning et al. (U.S. Patent No. 5,770,559) or vice versa. The rejection is traversed.

The claims are directed to a method for making drug-containing particulate product, and require a specific combination of process features, including: contacting a feed solution with a compressed anti-solvent fluid to precipitate drug-containing particles, the feed solution comprising the drug and a biocompatible polymer in a cosolvent system including at least a first organic solvent and a second organic solvent that are mutually soluable; and separating the drug-containing particles from the anti-solvent fluid; and the drug-containing particles include both drug and biocompatible polymer.

In the Office Action, the Examiner notes that Debenedetti et al. disclose a process for preparing protein microparticles using a supercritical anti-solvent fluid, and the Examiner recognizes that Debenedetti et al. do not teach that the feed solution for such processing contains a drug and a biocompatible polymer, as is required of the pending claims.

Debenedetti et al. disclose only the manufacture of substantially pure protein particulates by a disclosed supercritical anti-solvent precipitation technique, and do not disclose manufacture of multi-component particles that include both drug and biocompatible polymer using the disclosed supercritical anti-solvent precipitation technique. On the contrary, Debenedetti et al. disclose

making multi-component products only following pre-manufacture of protein particles by the anti-solvent precipitation process. Debenedetti et al. specifically disclose first making small particulate protein by supercritical anti-solvent precipitation, and then formulating the pre-manufactured particulate protein with a bioerodible polymer to prepare a dispersion of the particulate protein in a matrix of the bioerodible polymer. See, Debenedetti et al. at column 3, lines 24-40 and at column 6, lines 33-56. It is clear that Debenedetti et al. are making substantially pure protein particles by supercritical anti-solvent precipitation and then dispersing those protein particles in a polymer matrix to make multi-component products. As recognized by the Examiner, this teaching of Debenedetti et al. is substantially different than the method recited in the Claims that requires both drug and biocompatible polymer to be processed together in a feed solution that is contacted with a compressed anti-solvent fluid to produce multi-component particles comprising both drug and biocompatible polymer.

Manning et al. is directed to preparation of a true, homogeneous solution of a pharmaceutical substance dissolved in an organic solvent in which the pharmaceutical substance is not normally soluble. Solublization is achieved by forming a hydrophobic ion pair complex between the pharmaceutical substance and an amphiphilic material. In this way, Manning et al. are able to dissolve pharmaceutical substances, in the form of the hydrophobic ion pair complex, in an organic solvent in which the pharmaceutical substance would otherwise not be soluble. Manning et al. further discloses that although the solution containing the pharmaceutical substance, dissolved in the form of a hydrophobic ion pair, is itself a valuable product, the solution may also be used to prepare additional pharmaceutical products, including solid particles. One preferred processing technique disclosed by Manning et al. is to subject the solution to anti-solvent precipitation processing, using a near critical or supercritical anti-solvent fluid, to prepare powder of solid particles. See, Manning et al., in the abstract, at column 3, lines 1-23; at column 4, lines 45-51; and at column 11, lines 18 through column 12, line 24.

Manning et al. also disclose that the solution can be prepared to include a biodegradable polymer co-dissolved in the organic solvent along with the pharmaceutical substance and amphiphilic material, and that when processed by the gas anti-solvent precipitation, the particles produced comprise an intimate mixture of biodegradable polymer with the pharmaceutical substance

and amphiphilic material. See, Manning et al. at column 3, lines 24-35; at column 9, lines 5-52; and at column 14, lines 9-20. Manning et al. do not disclose the use of solvent systems that comprise multiple mutually soluble organic solvents. Rather, Manning et al. address solubility issues through use of hydrophobic ion pairing to alter the solubility characteristics of a pharmaceutical substance relative to a desired organic solvent.

Manning et al. disclose that the co-processing of the polymer and pharmaceutical substance is possible because with the pharmaceutical substance in the form of a hydrophobic ion pair complex, the pharmaceutical substance is soluble or easily suspendable in solvents that will also dissolve the biocompatible polymer. See, Manning et al., specifically at column 9, lines 33-36, where Manning et al. state:

> The present inventors have discovered that HIP complexes may be uniformly distributed in biodegradable polymers as they possess a solubility in solvents that will also dissolve the polymer. Where HIP complex does not dissolve in the solvent used it will suspend easily as a result of its hydrophobic surface.

Clearly, neither Debenedetti et al. nor Manning et al. disclose the method recited in the Claims, which claimed method involves anti-solvent fluid precipitation of drug-containing particles that also contain biocompatible polymer from a feed solution comprising both the drug and the biocompatible polymer in a cosolvent system with multiple mutually soluble organic solvents. Furthermore, neither reference bridges the teaching deficiency of the other in relation to the claimed subject matter.

The Examiner asserts that Debenedetti et al. disclose that "organic solvents are selected from at least one of ethanol, DMSO, dimethylamine and others." It is believed that the Examiner is referring to a disclosure by Debenedetti et al. at column 6, lines 18-22, where it is stated:

> Useful solutions for the protein comprise at least one non-aqueous solvent selected from the group consisting of ethanol, formamide, dimethylsulfoxide,

> tetrahydrofuran, acetic acid, dimethylformamide, ethylene glycol, liquid polyethylene glycol and demethylaniline. [Emphasis added.]

From this quote, it is clear the Debenedetti et al. are not specifying the use of solvent systems including multiple mutually soluble organic solvents. At most, Debenedetti et al. are stating that they are not excluding from their process the use of mixtures of the listed non-aqueous solvents. In any event the object clearly stated by Debenedetti et al. is to dissolve the protein to make substantially pure protein particles. Also, it is noteworthy that in the examples provided by Debenedetti et al., the solutions used include only a single organic solvent (ethanol) in a mixture of 90% of that organic solvent with 10% water. And again, the solvents identified by Debenedetti et al. are particularly specified for the protein, and not for a biocompatible polymer. Debenedetti et al. do not disclose or suggest in any way inclusion of a biocompatible polymer in a feed solution along with the protein that is processed by the supercritical anti-solvent precipitation. And this is not because Debenedetti et al. have not considered the use of a polymer. On the contrary, as discussed above, Debenedetti et al. specify that when a bioerodible polymer is used, it is mixed with the protein particles that have already been premanufactured by the supercritical anti-solvent fluid technique, whereby the premanufactured protein particles are dispersed within a polymeric matrix.

Conversely to Debenedetti et al., Manning et al. disclose including both a pharmaceutical substance and a biodegradable polymer in a single solution as feed to gas anti-solvent precipitation processing to prepare particles including both the pharmaceutical substance and the biodegradable polymer in an intimate mixture. The nature of the product prepared by Manning et al. (particles with intimate mixture of pharmaceutical substance and biodegradable polymer) is significantly different than the multi-component product disclosed by Debenedetti et al. (premanufactured protein particles dispersed in matrix of bioerodable polymer) and there is no indication that one of ordinary skill in the art would consider those two references in combination if attempting to prepare multi-component particles that contain both a polymer and a drug, because Manning et al. and Debenedetti et al. each specifically provide a complete process for preparing multi-component products, but of different types.

However, even if, for the sake of argument, one of ordinary skill in the art were to consider both Manning et al. and Debenedetti et al. in combination, such a combination would not render obvious the claimed invention. This is because based upon a combination of the references, it is clear that one of ordinary skill in the art would be motivated to approach the co-processing of a pharmaceutical substance and biodegradable polymer by using the co-dissolution technique of Manning et al., which uses a hydrophobic ion pair complex. There is no disclosure or suggestion leading one of ordinary skill in the art to modify the solubilization technique of Manning et al. (which effects co-solubilization of pharmaceutical substance and biodegradable polymer by forming a hydrophobic ion pair with the pharmaceutical substance) to use a feed solution of multiple mutually soluble organic solvents. Manning et al. already provide a complete process for co-processing a pharmaceutical substance and biodegradable polymer in a single feed solution.

Based on the foregoing, it is clear that independent Claim 26, and also the dependent claims under that independent claim, are not obvious under 35 U.S.C. §103 over Debenedetti in view of Manning et al., or vice versa.

Moreover, each dependent claim includes one or more additional limitations that, in combination with the other limitations of the claim or claims from which it depends, further distinguishes over Manning et al. and Debenedetti et al. For example, Claims 28-33 specify particular selections for the first organic solvent and the second organic solvent in the cosolvent system recited in Claim 26. Claim 28 requires that the first organic solvent is a polar solvent for the drug and the second organic solvent is a non-polar solvent for the biocompatible polymer. Claim 29 requires that the first organic solvent is substantially miscible with water and the second organic solvent is substantially immiscible with water. Claim 30 requires that the second organic solvent comprises at least one of methylene chloride, formaldehyde, dioxolane, chloroform, benzene, ethyl ether, toluene, xylene, 1, 3-dioxane and THF, Claim 31 further requires that the first organic solvent comprises an alcohol, Claim 32 further requires that the first organic solvent comprises a C_1-C_5 alkanol, and Claim 33 further requires the first organic solvent of Claim 32 and that the second organic solvent comprises methylene chloride. As another example dependent Claims 34 and 35 each further requires particular processing for preparing the feed solution and Claims 94-96 each further requires particular volume ratios of the second organic solvent to the first organic solvent. Neither of

Debenedetti et al. nor Manning et al., alone or in combination, disclose or suggest the subject matter of these more particular processing combinations. Moreover, new dependent Claims 106-109 have been added, which also further distinguish over Debenedetti et al. and Manning et al.

The rejection under 35 U.S.C. §103(a) should be withdrawn.

Rejections Based On Non-Statutory Obviousness-Type Double Patenting

The Examiner has rejected Claims 26-40 and 94-105 on the ground of non-statutory obviousness-type, double patenting with respect to Claims 1-29 of U.S. Patent No. 6,669,960 and Claims 1-55 of U.S. Patent No. 6,761,909.

With respect to the objection based on U.S. Patent No. 6,669,960, it is respectfully noted that Claims 26-40 were presented in and subject to a requirement of restriction in U.S. Patent Application No. 09/740,573, which issued as U.S. Patent No. 6,669,960. Because Claims 26-40 were subject to restriction with respect to the claims that ultimately were examined and issued in U.S. Patent No. 6,669,960, the rejection based on non-statutory obviousness-type double patenting is not proper under 35 U.S.C. §121 and MPEP §804.01, and should be withdrawn. For the Examiner's information, a copy is enclosed of an Office Action dated March 20, 2002 from prosecution of U.S. Application No. 09/740,573 showing the restriction requirement made during prosecution to obtain U.S. Patent No. 6,669,960. In U.S. Application No. 09/740,573, Claims 1-93 were subject to restriction into five groups: Group I Claims (1-25 and 45) were elected for prosecution in 09/740,573. Group II Claims (26-40) are being pursued in this application, which was filed prior to issuance of U.S. Patent No. 6,669,960. The specification is being amended herewith to note the relationship between this application and Application No. 09/740,573 as being a divisional. It is noted that when this application was filed, the claims were not limited to Claims 26-40, and, therefore, the application was not designated as a divisional. However, subsequent to filing, in a second Preliminary Amendment, the claims were limited to Claims 26-40, and new claims made dependent from Claim 26, but the cross-reference to related applications was not amended at that time to note the divisional status of this application.

With respect to the rejection based on U.S. Patent No. 6,761,909, a Terminal Disclaimer will be filed to obviate that rejection when allowable subject matter is otherwise identified by the

Examiner, and it is respectfully requested that the requirement for filing the Terminal Disclaimer be held in abeyance until that time.

It is believed that all of the issues raised in the Office Action have been addressed herein. Should the Examiner maintain any of the rejections under 35 U.S.C. §103(a) of any of the pending claims, it is respectfully requested that it be pointed out with particularity how the cited reference(s) meet each and every term of each claim with respect to which rejection is maintained. In the absence of a persuasive showing to that effect, all pending claims should be allowed.

If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Date: March 23, 2006

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